

Knowledge Sharing



and Co-operation

*Are these the key to a more certain future
for pharmaceutical innovation?*

Workshop Report

CMR INTERNATIONAL INSTITUTE FOR REGULATORY SCIENCE

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Workshop on Knowledge Sharing and Cooperation **Are these the key to a more certain future for pharmaceutical innovation?**

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Workshop Organisation

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WORKSHOP ON KNOWLEDGE SHARING AND COOPERATION: Is this the key to a more certain future for pharmaceutical innovation

Section 1: Overview

Background to the Workshop

Altruism or enlightened self-interest – what are the drivers for a more open research environment for medicines?

Several of the Workshops held by the CMR International Institute for Regulatory Science over the last five years have suggested ways that research into new medicines could benefit from a greater willingness to share the knowledge gained by the various stakeholders, above all where safety issues are involved.

This meeting was convened to take these discussions further and to look at the potential gains that more transparency would bring in terms of public perception of the pharma industry, the quality of regulation and, in particular, in increased patient safety and more efficient research.

Workshop highlights

The first Session of the Workshop addressed the impact of *Greater Knowledge Sharing* on pharmaceutical innovation, decision-making and patient safety and was chaired by **Dr Willard Dere**, Senior Vice President and International Chief Medical Officer, Amgen, UK.

Opening the meeting, Dr Dere spoke of the 'shared reality' faced by industry of the low productivity of current pharmaceutical research, in terms of new molecules and rising costs of development and the information explosion, enabled by the Internet. This was coupled with major trust issues as a perceived lack of transparency has eroded confidence in both pharma companies and the public institutions that regulate them.

He warned, however, that 'Total transparency is not an absolute good': Pharmaceutical research is competitive and excessive or premature demands for public disclosure may hamper creativity or be a disincentive for high-risk research.

Dr Jeffrey Cossman, Chief Science Officer, The Critical Path Institute (C-Path), USA discussed the role and remit of C-Path, which has been established to further the goals of *effective collaboration among government, academia and the private sector* expressed in FDA's *Critical Path Initiative* (CPI). Dr Cossman described the establishment of Consortia to address specific research issues, and highlighted the recent success of the *Predictive Safety Test Consortium* (PSTC) in agreeing seven validated biomarkers of kidney damage in pre-clinical studies on new compounds.

Professor Bruno Flamion, Chairman, EMEA Scientific Advice Working Party discussed the *Regulatory Role in opening up the Knowledge Base*, by reference to the way in which the European Medicines Agency (EMA) is working. Professor Flamion was of the view that regulatory bodies should not be in the driving seat for bringing about data sharing among companies but had an important role as partners in the process. The Scientific Advice process has the potential for disseminating information on broader issues, within the constraints of product-related confidentiality.

He discussed the *Innovative Medicines Initiative* (IMI), the pan-European Public-Private Partnership that has similarities to the US *Critical Path Initiative*. Its research agenda covers safety issues, such as improving predictions of immunogenicity, efficacy issues, such as pain research, and the overarching topic of strengthening benefit-risk monitoring for medicines.

Dr Craig Metz, Vice President, US Regulatory Affairs, GlaxoSmithKline, USA, discussed perceptions, progress and problems of bringing greater transparency into the clinical research process. Dr Metz described the legal requirements, in the US, for a public registry of clinical trials and the implications of forthcoming changes to include the outcomes of studies. His account of GSK's own clinical trials database included a study of statistics on 'visits' to the website. Although there is a high proportion of transient visits, the number of 'meaningful' site interactions (length of time and number of pages visited) has exceeded 50,000 since launch in 2005.

Professor Tim Hammond, Vice President, AstraZeneca, UK gave a company viewpoint on sharing pre-clinical data, especially where safety issues are involved that could have implications beyond the specific compound being studied. Whilst competitive factors must be acknowledged – the possibility of giving an advantage to another company in a 'race' – there are ethical drivers that should be a higher priority when safety is an issue. Sharing unpublished findings 'for the good of science' should also be a driver, he suggested.

Whilst there is an onus on companies to be more open, regulators also hold the key as they already have access to all data submitted. This could be further enhanced by access to data on discontinued projects since sharing relevant knowledge could help prevent wasteful research projects on concepts and mechanisms that are doomed to fail.

Openness is risky but necessary. Companies that develop cultures based on secrecy may ultimately hamper the all-important ability to collect new ideas outside of their environments. *William Dere, quoting with reference to Alph Bingham, CIO.com*

Dr Andrew French, *Group Manager Licensing Division, MHRA, UK* gave a regulatory perspective on sharing research data and referred to the aftermath of 'TGN1412 incident' in March 2006 that had led to a call for a database of safety information from unpublished preclinical studies and phase one clinical trials. This has not yet been progressed because of practical difficulties of ownership and maintenance but Dr French noted the progress that has been made in the exchange of information between regulators by establishing memoranda of understanding.

Introducing Session 2 on *Facilitating co-operation and knowledge sharing*, **Dr Supriya Sharma**, *Director General, Therapeutic Products Directorate, Health Canada* drew a geographical analogy with the reaction, when under stress, of looking inwards and building walls rather than outwards and building bridges. She was encouraged by the apparent willingness to build the necessary bridges to make greater information sharing a reality.

Dr Liam Ratcliffe, Senior Vice President, Neurosciences, Pfizer Inc, USA reviewed the current boom in pharmaceutical precompetitive consortia and the common challenges they face, including legal/IP issues, governance and decision-making, logistics, operation and delivery. Dr Ratcliffe emphasised the importance of regulatory involvement in consortia in order to improve acceptance of the output through early endorsement and engagement.

The Workshop programme included a presentation by **Dr Joanne Meyer**, *Vice President and Global Head, Biomarker Development, Novartis Pharmaceuticals, USA*, reporting on her company's experience of biomarker consortia. Although bad weather and cancelled flights prevented her participation, Dr Meyer had provided a comprehensive slide handout which gave insight into the Novartis' work with the C-Path Predictive Safety Testing Consortium Nephrotoxicity Working Group.

RECOMMENDATIONS AND CONCLUSIONS

The final Session, under the Chairmanship of **Dr Murray Lumpkin**, *Deputy Commissioner (International and Special Programs), FDA, USA* received reports from the Syndicate groups which had discussed the need for greater knowledge sharing and cooperation from two perspectives: **Safety**, and **Clinical development**.

Pre-clinical safety

There are increasing moves (both voluntary and through legislation) to establish registries of clinical trials and there was a view that similar databases of preclinical data would be the next step in trying to improve transparency and dispel the image of secrecy and concealment in pharma research.

It was agreed, however, that mandatory public reporting of all pre-clinical studies was not a viable option or good use of resources and would merely add to the current 'information overload'.

There was, instead, a **recommendation** for a mechanism whereby a forum of interested parties should be established by companies and/or agencies as a 'Safe Haven' for discussions when a potential safety issue had been identified that had wider implications for other products (e.g., through a structural relationship or through a mechanism of action).

It was further recommended that the procedure should be formalised through the development of ground rules, with guidelines for identifying issues and a template for reporting the outcome. It was suggested that this might be a role for the CMR International Institute.

Clinical development

There were similar concerns that the information being made available on clinical studies is largely uncollated and issues might be missed, especially from terminated studies that could have wider research implications. Collecting, analysing and organising such information would, however, take a great deal of effort and resource.

It was therefore proposed that a survey should be undertaken to determine the use of information on clinical research that is already being made available to the public via industry and authority websites.

Knowledge of disease Management

There were concerns that valuable 'indirect' information (e.g., placebo results, pharmacogenetic data) is being lost, especially when projects are terminated and **it was agreed that** opportunities should be created for breaking down traditional 'silos' of information and making sure that it is much more broadly available across medical and scientific communities.

Cooperation between different stakeholders

There was strong support for the increasing establishment of both private-public funded development programmes and consortia that look at disease areas and discuss potential therapeutic strategies at a pre-competitive stage of development. It was observed that unmet medical need is the key driver for such initiatives but there were some concerns that 'non-traditional' players may be underestimating the regulatory aspects of the undertakings

Review and Reimbursement

This was discussed as a special case where better cooperation and coordination of activities could be of significant benefit in making new medicines available to patients. Historically, the regulatory review and the health technology assessment (HTA) for reimbursement have been kept as separate exercises but the two processes are starting to overlap resulting in duplication of effort and introducing an additional uncertainty into research decisions.

It was recommended that the CMR International Institute should develop a white paper to address the implications of an increased alignment between regulatory and HTA processes.



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Section 2: Outcome

Syndicate Discussions

Session 3 of the Workshop, during which the Syndicate discussions took place, was chaired by **Dr Murray Lumpkin**, *Deputy Commissioner (International and Special Programs), FDA, USA*.

The Workshop participants formed two Syndicate groups to address 2 topics:

- **Topic A: SAFETY - Learning from failures and sharing the ‘science of toxicity’**
- **Topic B: CLINICAL DEVELOPMENT - Sharing scientific and regulatory knowledge to improve therapeutic progress**

The Chairpersons and Rapporteurs for the two groups were:

Syndicate 1	<p><i>Chair:</i> Prof Robert Peterson, <i>Clinical Professor of Paediatrics, University of British Columbia Faculty of Medicine, Canada</i></p> <p><i>Rapporteur:</i> Dr David Jefferys, <i>Vice President, Global Regulatory, Eisai R&D Co Ltd, UK</i></p>
Syndicate 2	<p><i>Chair:</i> Prof Sir Alasdair Breckenridge, <i>Chairman, Medicines and Healthcare products Regulatory Agency (MHRA), UK</i></p> <p><i>Rapporteur:</i> Dr Paul Huckle, <i>Senior Vice President, US Regulatory Affairs, GlaxoSmithKline, USA</i></p>

1. BACKGROUND

Dr Neil McAuslane introduced the Syndicate discussions with an overview of some of the conclusions and recommendations from previous Institute Workshops that had led to the decision to convene the current discussions on sharing knowledge and cooperating in the better use of information on the development of new medicines:

- Concerns that there is a *wealth of knowledge and experience contained in the closed files held by the regulatory agencies but confidentiality constraints prevent this from being shared* was expressed in 2003¹ and the issue of confidentiality constraints was one that the Syndicates were specifically asked to address.
 - Primary objectives for sharing this data would be to avoid waste of resources and the address the ethical issues involved in allowing companies to pursue research where the agencies have knowledge of specific hazards or where the undertaking is known to be a ‘blind alley’.
- The value of the consortium approach to the development and validation of biomarkers was endorsed by participants at the Biomarkers Workshop in 2006² who pointed to the need for a directory of information on current and future consortia and the scope of their activities.
- The Workshop on Decision-Making, in 2006³, also called for a greater *willingness to share data* particularly on products that have run into toxicity problems and on projects that have

¹ Institute Workshop on Regulatory Performance, September 2003

² Institute Workshop on New Technologies and Biomarkers: The Way Ahead - May 2006

Copies of Institute reports are available from institute@cmr.org

³ Institute Workshop on Quality Decision-Making - December 2006

been terminated before registration. Such exchange should be between companies and also between companies and agencies.

- It was acknowledged, however, that there is little interest in following-up terminated projects, at a scientific level or in publishing results but independent research could be valuable.
- When early clinical testing was discussed in 2007⁴, there was strong support for the recommendation in the Expert Scientific Group (Duff report) that *Regulatory authorities should consider ways to expedite the sharing of safety information on phase one clinical trials between regulators within the EU and worldwide* and there was discussion on whether the Institute could support such an initiative by carrying out a study among pharmaceutical companies to determine their views and current practices in relation to transparency in sharing information on research projects that fail at an early stage for safety reasons.
- There was also discussion of the possibility of a 'blinded' database of compounds that fail in the pre-clinical or early clinical stages for safety reasons. The database would primarily be a resource for regulators but the level of feedback to companies would also need to be agreed.
 - It was observed that *there is public pressure and an expectation that regulatory agencies would have access to this information order to fulfil their role in protecting public health. Where safety issues are concerned, commercial confidentiality is unlikely to be accepted as a valid argument.*

Several of these themes were followed up in the current discussions and one of the issues that both Syndicates were asked to address were the ethics (see last bullet point) of making information related to safety more widely available. Dr McAuslane suggested that the Syndicate discussions should reflect three tenets that had also emerged from the Workshop presentations:

- Changes are needed in the research, development and review paradigm if pharmaceutical research is to remain sustainable but more open cooperation between and among companies and agencies will be required to achieve such changes;
- There are both individual and mutual benefits to be gained by companies from greater information sharing;
- Greater public and political understanding and trust in the processes for developing new medicines and regulatory decision-making requires action to improve transparency.

2. SUMMARY OF RECOMMENDATIONS AND CONCLUSIONS

2.1 Pre-clinical safety issues: 'Safe Havens' for discussing new and emerging issues

Valuable safety information about the testing and development of new medicines is being lost because there are no specific mechanisms for collecting and collating related safety issues that arise from projects that are terminated in the pre-clinical stage.

- **It was recommended** that a mechanism should be developed whereby companies and/or agencies could convene a forum of interested parties when there is reason to believe that a safety issue has been identified with wider implications for other products (e.g., through a structural relationship or through a mechanism of action).
- **It was further recommended** that the procedure should be formalised through the development of ground rules, with guidelines for identifying issues and operating the procedure, and a template for reporting the outcome. The establishment of the framework

⁴ Institute Workshop on Rethinking Early Clinical Testing, April 2007
Copies of Institute reports are available from institute@cmr.org

for convening such 'safe haven' forums and reporting the outcome could be a role for the CMR International Institute.

- A '**Safety Issues database**' should then be set up to collect the outcome of investigations from these procedures which would be available to inform both research workers and regulatory agencies that might encounter similar issues in future development projects.

2.1.2 Pre-clinical toxicity-testing database

It was agreed that a mandatory database or registry of all pre-clinical toxicity studies is **not** a viable or useful option for collecting and reporting data on research relating to the development of medicinal products, carried out by pharmaceutical companies or other research organisations.

This would merely add 'information overload', not be a good use of resources and might encourage misuse and misinterpretation by factions hostile, for example, to research using animals.

2.2 Greater transparency on safety issues in clinical development

Increasing amounts of information are being made available on clinical studies but there are concerns that collated information is not easily available to identify trials that are terminated, especially in the early phases, and that issues might be missed that could have wider research implications. Collecting, analysing and organising such information would, however, take a great deal of effort and resource and it would first be important to ensure information made publicly available reaches, and is used by the right target users.

It was proposed that a survey should be undertaken to determine the use of information through clinical trial registries and databases that is already being made available to the public via industry and authority websites.

2.3 Regulatory Role: Sharing Scientific Advice

There are potential advantages that go beyond individual company interests, in allowing greater sharing of information and issues arising from discussions with agencies as part of Scientific Advice or the review of applications.

It was observed that a greater willingness, on the part of companies, to release such information would reduce the burden on agencies of removing confidential items from the data (redaction) in order to meet the increasing number of requests under freedom of information (FOI) laws.

2.4 Knowledge of disease Management

Opportunities for improved disease management are being missed because information that is an 'indirect' product of development programmes (e.g., placebo results, pharmacogenetic data) is not being shared, especially when projects are terminated.

It was agreed that opportunities should be created for breaking down traditional 'silos' of information and making sure that it is much more broadly available across medical and scientific communities.

2.5 Cooperation between different stakeholders

2.5.1 Public – Private funded/directed development programs

There is an increasing use of private-public funded and directed development programmes and these approaches are welcomed.

It was noted, however, that some 'non-traditional' players may be underestimating the regulatory aspects of the undertakings

2.5.2 Cooperation in development

It was observed that unmet medical need is the key driver for the establishment of consortia to look at disease areas and discuss potential therapeutic strategies at a pre-competitive stage of development.

The consortia approach, however, has additional potential in more general scientific methodologies such as benefit-risk models and adaptive study designs.

2.6 Review and Reimbursement: A special case for better coordination

Historically, the regulatory review and the consideration of products for listing and reimbursement by health care providers (*health technology assessment* – HTA) have been kept as separate exercises. The two processes are, however, starting to overlap resulting in duplication of effort and introducing an additional uncertainty into research decisions.

It was recommended that the CMR International Institute should develop a white paper to address the implications of an increased alignment between regulatory and HTA processes.

3 DISCUSSION OF THE RECOMMENDATIONS AND CONCLUSIONS

General points

The Syndicates had been asked to address the question '*How can the development and registration of new medicines or therapies be made more efficient through a cooperative approach to designing research programmes and regulatory models*'. In fact, the first question to ponder was not 'how' this can happen but whether it can happen at all.

Whilst there was general optimism that R&D could benefit from a greater willingness to share experiences that might, historically have been regarded as 'trade secrets' there was also a need to be realistic about the competitive nature of pharmaceutical research. The 'race' to be first-in-class in a new therapeutic area is increasingly important and the difficulties of convincing senior management to 'step from the pack' and take a lead in releasing more information should not be underestimated.

Many believed, however, that greater disclosure, particularly of pre-clinical information, was inevitable and the question that remains is whether industry will be proactive and take a lead, or will only act in response to the next crisis and the coercion of legal requirements.

Drivers and caveats

The Syndicate discussions encompassed practical, ethical and resource considerations including the following:

- **Transparency vs. information overload.** Industry should respond to criticism and public distrust but only by providing information that is meaningful and not by 'transparency for its own sake' that obscures vital particulars in a deluge of uncoordinated information.
- **Reducing waste** should be an overall objective. Focused and targeted knowledge sharing should help companies avoid duplicative animal testing or unnecessary expenditure and exposure of patients when a particular line of investigation is known to be a 'blind alley'.
- **Company commitment:** Pooling information and participation in consortia will only work if there is confidence between companies that all parties are coming to the table to provide information and not just to gain knowledge for their own advantage.
- **Misuse of information:** One of the risks of releasing more and earlier information into the public domain is that it will be misuse and misinterpreted by third parties and used out of context and/or in flawed analyses.

- **Public perception of risk** is an issue that goes beyond medicines and needs to be seen in the context of a wider debate on, for example, aviation, road transport and nuclear power that require educational programmes at the level of governments

3.1 Pre-clinical safety issues: 'Safe Havens' for discussing new and emerging issues

Recommendation

A mechanism should be developed whereby companies and/or agencies could convene a forum of interested parties when there is reason to believe that a safety issue has been identified with wider implications for other products (e.g., through a structural relationship or through a mechanism of action).

The pre-clinical toxicity testing of medicines does not involve the regulatory agencies until there is a decision to test a new product in humans. Consequently, there are no requirements to report tests carried out on products that fail for safety reasons or projects that are abandoned for other reasons.

Although the concept of a non-selective database of all such studies was rejected (see 3.1.2) it was felt that there should be a mechanism to bring forward and share emerging issues from failed pre-clinical studies that may have implications beyond the substance or series of substances tested.

Procedure

The following stages were envisaged:

- *Signal identification*: Safety reasons for pre-clinical termination of a project that could impact pharma-research in a wider context;
- *Call for interested parties*: procedure for alerting other researchers that may be working in the same field;
- *Convening a group of stake holders* to address the specific issue (other companies, regulatory agencies, academics etc);
 - *Determine the 'ground rules'* for the discussions: Anti-trust, intellectual property issues etc.
- *Agree a reporting procedure* at the end of the discussion.

Competition issues

It was recognised that there would be issues of commercial sensitivity in deciding that an issue should be brought forward for discussion in a 'Safe Haven' forum. The procedure is unlikely to be followed, for example if the development of related back-up compounds is in progress.

The main motivation would be to identify areas where highlighting or resolving an issue could:

- Lead to an improvement in the efficiency of the research process for the good of industry as a whole;
- Be driven by ethical issues: To prevent others from investing resources (human, animal and material) in research that leads down a 'blind alley' with potential safety implications.

Precedents for company collaboration

There are examples where companies have set aside individual commercial interests and collaborated on issues where a general safety or research issue was involved.

The examples cited (from pre- and post- clinical phases) were:

- *Length of toxicity studies*: The study of 6 vs. 12 month toxicity requirements carried out by CMR International to support the ICH guideline S4⁵;
- *QT Prolongation*: Data provided by companies to assist the development of ICH Guideline S7B⁶;
- *PPAR agonists*: Companies provided data to FDA on glitazones in response to concerns about cardiovascular effects
- *Replacement of CFCs*: Industry consortium to develop safe solutions for medicinal products when chlorofluorocarbons (CFCs) were banned in aerosols on environmental grounds

Recommendation

The 'Safe haven' procedure should be formalised through the development of ground rules, with guidelines for identifying issues and a template for reporting the outcome of discussions. The establishment of the framework for convening such 'safe haven' forums and reporting the outcome could be a role for the CMR International Institute.

It was acknowledged that there were ownership and leadership issues with the 'Safe Haven' proposal. Companies could initiate individual procedures but there may be scope for involving other bodies, for example industry associations or professional societies.

A first step, however, would be for an organisation such as the CMR International Institute for Regulatory Science to initiate a project to lay down some ground rules for the procedure, in particular:

- Guidance on identifying issues that might be discussed and reported;
- A template for reporting pre-clinical findings that indicate a safety problem;
- Guidance on public reporting of the outcome:
 - Amount of information, level of detail, potential pitfalls

Observation

One potential product would be a 'Safety issues database' to collect the outcome of similar investigations which would be available to inform both research workers and regulatory agencies that might encounter similar issues in future development projects.

In order to be useful, prospectively to a wider body of researchers it would be necessary to make the aggregated reports of 'Safe Haven' forums available in some sort of database. There was discussion of the availability of this data and the potential for misuse as well as the positive benefits of improving the industry's image for transparency.

It was agreed that, in the current environment, a closed database was not an option as it would increase the 'paranoia' that industry has secrets to keep behind closed doors. The information would show the 'negative' side of pharma research but it was pointed out that the balancing information on successful compounds is already reported in public documents (EPARs etc) when products are marketed.

⁵ Guideline S4 on the *Duration of Chronic Toxicity Testing in Animals (Rodent and Non-Rodent Toxicity Testing)* adopted by the International Conference on harmonisation (ICH) in 1998.

⁶ Guideline S7B on *The Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals* adopted by the International Conference on harmonisation (ICH) in 2005

ICH guidelines are available from www.ich.org

3.1.2 Pre-clinical toxicity-testing database

It was agreed that a mandatory database or registry of all pre-clinical toxicity studies is **not** a viable or useful option for collecting and reporting data on research relating to the development of medicinal products, carried out by pharmaceutical companies or other research organisations.

The possibility was discussed that there might be calls for a legal requirement to create a registry of all pre-clinical studies carried out on medicinal compounds, in the way that clinical trial registries are becoming mandatory.

It was strongly agreed that this would be 'transparency for its own sake' leading to an unusable overload of information that could not be justified in terms of expense and resources but which would merely add to the overall cost of pharmaceutical R&D.

It was noted that databases of failed compounds exist, for example the within the CMR International Global R&D Programme. This, however, captures data only from participating multinational companies and would not include failed compounds investigated and abandoned outside global development programmes by small to medium-sized enterprises (SMEs) and venture capital companies.

3.2 Greater transparency on products terminated during clinical development

Recommendation

Concern was expressed about a lack of transparency of data on terminated projects, especially early phase clinical studies where there could be implications for other research products. Before extending current data resources, however, a survey should be undertaken to determine the use of information on clinical research that is already being made available to the public via industry and authority websites.

Posting information on clinical trials in a public registry is mandatory in the US and many companies include databases of clinical trial information on their websites. In addition, the World Health Organization as well as industry trade associations have set up internet portals that give access to registries and databases of clinical trial information (see Box 1).

Box 1: Examples of public access to clinical trial information

US National Institute for Health

Registry of ongoing trials by companies, government agencies and academia (participation is obligatory under FDAAA 2007) <http://clinicaltrials.gov/>

International Federation of Pharmaceutical Manufacturers & Associations:

IFPMA Clinical Trials Portal giving access to information from registries and databases established by companies, government bodies, industry associations and biomedical publishing companies

www.ifpma.org/clinicaltrials

Pharmaceutical Research and Manufacturers of America (PhRMA)

Clinical study results from over 60 companies <http://www.clinicalstudyresults.org/>

The Association of the British Pharmaceutical Industry (ABPI).

Managed by CMR International and initiated by the ABPI

Registry of retrospective Phase III and on-going Phase IV Clinical Trials conducted in the UK;

<https://www.cmrinteract.com/clintrial/>

Japanese Pharmaceutical Manufacturers Association (JPMA).

Japan Pharmaceutical Information Center registry of ongoing Japanese clinical trials

<http://www.clinicaltrials.jp>

World Health Organization

International Clinical Trials Registry Platform (ICTRP) Established with the ultimate objective of creating a 'one-stop search portal for searching registers worldwide'. Current registries are primarily government sources (Australia/New Zealand, China, India, The Netherlands, Sri Lanka)

<http://www.who.int/ictrp/en/>

The extent to which the outcome of clinical trials is reported varies and there were concerns about the availability and transparency of information on clinical trials that are terminated, especially in the early phases, because of safety issues. Although requirements in the US are being extended to include the outcome of clinical trials (FDAAA 2007⁷) but this may only add to the volume of information without making it easier to identify and collate common safety issues.

Collecting, analysing and organising such information would take a great deal of effort and resource and hence the recommendation that it would first be important to ensure that the information reaches the right target users.

The need for greater transparency

Regulatory requirements for clinical trial registries were originally driven by the belief that companies were carrying out trials that were not being reported adequately. There would be obvious advantages, for the industry's image, in a 'proactive' extension of this to identify cross-cutting safety issues which could help others avoid redundant research and reduce patient exposure to potential safety hazards.

Data that is being lost

Potentially valuable information resources are currently being archived and lost to the wider research community:

- Data from projects that are closed down are not in an appropriate format for sharing and to triage the information would be resource intensive:
 - Research teams are disbanded and re-assigned rapidly and the 'context' of the abandoned project is lost.
- Companies are concerned about giving away competitive advantage: pre-competitive areas are poorly defined:
 - As for products at a pre-clinical stage, there may be follow-on compounds in the pipeline;
 - The abandoned product might be resurrected later to investigate new indications and the IP aspects could be compromised by earlier disclosures.
- The reasons for abandoning a project are usually multifactorial. Terms such as 'commercial reasons' can obscure safety or efficacy issues with wider implications that may be missed.
- Investigators, ethics committees and patients are informed when trials are discontinued but this is not carried out in a structured or coordinated way that would capture the relevant information.

Legal concerns

There were concerns that placing unpublished information in the public domain could provide a 'loophole' for other parties seeking to circumvent data exclusivity constraints. TRIPS, for example, only provides protection for 'undisclosed' information⁸. Whilst a legal solution would be desirable it was acknowledged that, particularly in Europe, opening up a much wider debate on IP and generic competition etc.

⁷ Food and Drug Administration Amendments Act of 2007, available via www.fda.gov

⁸ World Trade Organization (WTO) Trade-Related Aspects of Intellectual Property Rights (TRIPS), Section 7: *Protection of undisclosed information*, in particular, Article 39.3. 'Members, when requiring, as a condition of approving the marketing of pharmaceutical or of agricultural chemical products which utilize new chemical entities, the submission of undisclosed test or other data, the origination of which involves a considerable effort, shall protect such data against unfair commercial use....'

3.3 The Regulatory Role: Information from scientific advice and applications

Observation

There are potential advantages that go beyond individual company interests, in allowing greater sharing of information and issues arising from discussions with agencies as part of Scientific Advice or the review of applications. A greater willingness, on the part of companies, to release such information would reduce the burden on agencies of removing confidential items from the data (redaction) in order to meet the increasing number of requests under freedom of information (FOI) laws.

In providing Scientific Advice, regulatory agencies have access to a unique store of information that could provide insight into emerging and cross-cutting research issues. Information on safety issues, if shared, could avoid patients in similar or future trials being put at risk and information on efficacy testing could prevent other companies from wasting resources on 'blind alley' research.

It was acknowledged that regulatory agencies have a network for the exchange of information where confidentiality agreements exist and that, in the interests of public safety, alerts about serious safety issues would be made known to other authorities.

Freedom of information

The fact that information is on file with agencies, through scientific advice or in archives of application data leaves them open, especially in the EU and USA, to requests under FOI laws. To comply with such requests, information needs to be redacted which is time consuming and resource-intensive and will ultimately increase the costs and/or reduce the efficiency of the review process. If industry is not willing to make information more readily available it merely pushes the problem further down the line.

3.4 Knowledge of disease Management

Observation

Opportunities for improved disease management are being missed because information that is an 'indirect' product of development programmes (e.g., placebo results, pharmacogenetic data) is not being shared, especially when projects are terminated. Opportunities should be created for breaking down traditional 'silos' of information and making sure that it is much more broadly available across medical and scientific communities.

Research into disease management extends across a much broader medical and scientific community than the work carried out by the pharma industry and there is a need for greater sharing of the information that arises directly and indirectly from such research.

Examples include:

- Non-responders and enhanced responders when using existing therapies
- Differences in the size of effects in different patient populations
- Geographical differences highlighted by the trend towards multinational clinical development programmes.

Placebo response

Of particular importance is the information that could be gained on disease modelling and tracking the natural history of disease by accumulating data from patients receiving placebos in studies on new medicines.

3.5 Cooperation between different stakeholders

3.5.1 Public – Private funded/directed development programs

Observation

There is an increasing use of private-public funded and directed development programmes and these approaches are welcomed. There was concern, however, that some 'non-traditional' players may be underestimating the regulatory aspects of the undertakings

Examples of private-public partnerships that were discussed included:

- The US Department of Health and Human Services (HHS) initiatives to encourage the development of a pandemic flu vaccine. This provides funding for targeted development activities and HHS are liaising directly, on an individual basis, with key vaccine manufacturers.
- The Ministry of Health, Labor and Welfare (MHLW) in Japan has been working, with local industry, on a similar objective but, in this case, companies have worked collectively, as a group.
- Privately funded, non-government initiatives under, for example, the Gates Foundation and the Rockefeller Foundation where research in specific disease areas is supported and directed.

Key features of this type of cooperative development are that the initiatives are driven by public health concerns where there is a high potential risk in that much money could be invested without achieving a successful outcome. In the case of vaccines, there is a high demand situation with large volumes being required in a short time scale. Such initiatives also operate in areas that are highly sensitive for industry, where failure would be politically unacceptable, and hence there is a need for government or other bodies to step in.

Other features in these sorts of initiatives are that all participants receive some recompense for working in the area whether it succeeds or fails. It was thought that this approach could be extended to other vaccines or to treatments where there is a specific health concern to be addressed.

It was, however, observed that the increasing use of Foundation funding models means that the 'non traditional' drivers for pharmaceutical development may be underestimating the regulatory aspects of some of these undertakings and not considering the broader view of how they are going to be dealt with, in the regulatory frameworks.

3.5.2 Cooperation in development

Observation

Unmet medical need is the key driver for the establishment of consortia to look at disease areas and discuss potential therapeutic strategies at a pre-competitive stage of development. The consortia approach, however, has additional potential in more general scientific methodologies such as benefit-risk models and adaptive study designs.

The value of the Consortia approach for addressing very specific issues in medical and disease research was recognised and reference was made to examples, from the Workshop, of consortia of interested parties for sharing information on neurodegenerative diseases⁹.

An advantage of such consortia is that they can produce consensus on best practice that are much more likely to be acceptable to agencies than a proposal from a single party or company.

⁹ CPI Opportunities List: Imaging Biomarkers in Neurocognitive Diseases and the *Measurement and Treatment Research to Improve Cognition in Schizophrenia* (MATRICS) consortium discussed by Dr Liam Ratcliffe, Pfizer, in Session of the Workshop (see Section 3 of this report).

Regulatory agency involvement

There was discussion about the impact on regulatory agencies of participation in consortia. It is important that agency staff are involved in such initiatives but the following were noted:

- *Conflict of interest:* Participating agencies must maintain a degree of independence as they would be called on to help propose solutions and then act as the ‘judge’ of whether those solutions are acceptable from a regulatory perspective when they are presented in a subsequent application;
- *Resources:* There is unlikely to be sufficient regulatory resource to meet the demands of the growing number of invitations to participate in consortia, which will result in difficult questions of which topics to support and which to decline.

CPI/IMI cooperation

Reports to the Workshop had indicated similar areas of interest between the US CPI and the EU Innovative Medicines Initiative (IMI)¹⁰ with a potential for overlap. The importance of good communication between the two initiatives was recognised in order to ensure that there is alignment and synergy in their activities and not duplication, with, for example similar exercises being carried out in parallel.

Wider remit of consortia

Sharing non-competitive information that is not compound- or product-specific could help researchers unlock the underlying biology of disease and validate targets. This includes validation of targets and approaches in clinical pharmacology that seek responses of products in new therapeutic areas. The qualification of biomarkers is a major area: Without widespread acceptance of validated biomarkers the need for long term outcome studies will remain but this is a classic example where a much broader engagement and interaction than single-company results in order to achieve regulatory acceptance.

A consortium approach to the development and verification of scientific models with broader application should also be encouraged. Examples include new clinical testing techniques such as adaptive study designs and models for benefit-risk assessment. There appear to be fewer concerns that these have competitive implications and there is therefore the potential to develop a longer list of areas in which to explore cooperative working.

3.6 Review and Reimbursement: A special case for better cooperation

Historically, the regulatory review and the consideration of products for listing and reimbursement by health care providers (*health technology assessment* – HTA) have been kept as separate exercises. The two processes are, however, starting to overlap resulting in duplication of effort and introducing an additional uncertainty into research decisions.

It was recommended that the CMR International Institute should develop a white paper to address the implications of an increased alignment between regulatory and HTA processes.

The current juxtaposition of regulatory approval and health technology assessment was seen as a prime example of an area where there is growing duplication of work and assessments that could be addressed through a more cooperative approach and information sharing. In many countries the HTA is becoming closer and closer to the regulatory assessment in both timing and scope, whereas, in the past, it was seen as a completely different exercise.

Examples were cited of:

- The UK agency NICE¹¹ offering, during the development phase, ‘scientific advice’ on how to achieve some of their requirements;

¹⁰The CPI was discussed by Dr Jeffrey Cossman and the IMI was discussed by Professor Bruno Flamion in Session 1 of the Workshop (see Section 3 of this report).

¹¹ NICE: now called the National Institute for Health and Clinical Excellence

- HTA agencies carrying out their own benefit-risk assessments on a limited body of evidence as they do not have access to the full regulatory file.

Differences in approach also include the way HTA agencies place greater emphasis on quality of life studies and it was noted that the 'payers' are encouraging moves to drive technical assessments back earlier into the development phase.

In the current situation, companies are finding that the regulatory outcome of a research project is much easier to predict than the HTA outcome and the uncertainty of whether a regulatory 'success' will fall at the 'fourth hurdle' of reimbursement is becoming a major issue in the companies' decision-making processes¹².

Examples from current practice

Canada: It was noted that a pilot project is being undertaken in Canada to carry out a parallel assessment between the agency (TPD) and the technical assessment group in which the HTA group have access to information and insights from the ongoing regulatory review. There will also be retrospective and prospective studies to try to achieve a better understanding between the two groups.

Taiwan: The Taiwanese agency has responsibility for both the regulatory review and the HTA of products. These assessments are carried out by different staff, but within the same organisation.

EU: The anomalous situation in the EU was noted whereby the centralised procedure reviews new medicinal products and approves them for marketing in all member states but the assessment for reimbursement and actual availability through national health schemes and insurance is carried out at national level, currently without harmonisation or regional consensus.

White paper

The recommendation for the CMR International Institute to develop a white paper was felt to be timely in order to address the many emerging issues, including:

- The need to rationalise regulatory agency and HTA agency requirements to avoid or minimise duplication;
- Ways to avoid the waste of research resources arising from different outcomes from a regulatory and HT assessments
- The public distrust and lack of understanding of a system that approves products as safe and effective one day but denies their availability under reimbursement schemes, the next.

The paper should also look at the industry 'position' that has, historically, sought to keep the scientific assessment separate from discussions of pricing and reimbursement and discuss the implications of continuing with the current models versus achieving greater integration and coordination.

¹² See also the report of the Institute Workshop on *Regulation and Reimbursement*, January 2008, available to member companies and regulatory agencies from institute@cmr.org

Annex 1

WORKSHOP PROGRAMME

SESSION 1: GREATER KNOWLEDGE SHARING - THE POTENTIAL IMPACT ON PHARMACEUTICAL INNOVATION, DECISION MAKING AND SAFETY	
Chairman's introduction	Dr Willard Dere , <i>Senior Vice President and International Chief Medical Officer, Amgen, UK</i>
Companionship on the Critical Path	Dr Jeffrey Cossman , <i>Chief Science Officer, The Critical Path Institute, USA</i>
What is the Regulatory Role in opening up the Knowledge Base?	Professor Bruno Flamion , <i>Chairman, EMEA Scientific Advice Working Party</i>
Clinical Research Transparency: Perceptions Progress and Promises	Dr Craig Metz , <i>Vice President, US Regulatory Affairs, GlaxoSmithKline, USA</i>
Sharing research data in the interests of safety	
Sharing pre-clinical data: 'To share or not to share' - a company viewpoint	Professor Tim Hammond , <i>Vice President, AstraZeneca, UK</i>
Sharing research data: an agency viewpoint	Dr Andrew French , <i>Group Manager Licensing Division, MHRA, UK</i>
SESSION 2: FACILITATING CO-OPERATION AND KNOWLEDGE SHARING	
Chairman's introduction	Dr Supriya Sharma , <i>Director General, Therapeutic Products Directorate, Health Canada</i>
Increased co-operation as the key to developing clinical and regulatory pathways for new disease treatments	Dr Liam Ratcliffe , <i>Senior Vice President, Neurosciences, Pfizer Inc, USA</i>
Safety Biomarkers for Regulatory Decision Making	
Experience from the Novartis-FDA-CRADA and Engagement with the Predictive Safety Testing Consortium	Dr Joanne Meyer , <i>Vice President and Global Head, Biomarker Development, Novartis Pharmaceuticals, USA</i> <i>(Participation cancelled due to transportation problems – slides and synopsis provided)</i>
SESSION 3: SYNDICATE DISCUSSIONS	
Chairman	Dr Murray Lumpkin , <i>Deputy Commissioner (International and Special Programs), FDA, USA</i>
Feedback from the Syndicates	<i>See Section 2 of this report</i>

WORKSHOP ON KNOWLEDGE SHARING AND COOPERATION: SECTION 3: SUMMARY OF PRESENTATIONS

SESSION 1: GREATER KNOWLEDGE SHARING - THE POTENTIAL IMPACT ON PHARMACEUTICAL INNOVATION, DECISION-MAKING, AND SAFETY

Chairman's Introduction

Dr Willard Dere

Senior Vice President and International Chief Medical Officer, Amgen, UK

Dr Dere opened the workshop with a reminder of the 'shared reality' that faces industry in the development of new medicines. One part of this reality is the major productivity crisis in terms of output of new molecular entities and the rising cost of R&D. A more optimistic element is the explosion of research data and information making this a most exciting age from a scientific perspective. Yet there are serious issues of trust surrounding the work of industry, which have been fuelled by a lack of transparency. Furthermore there are issues of the credibility of public institutions that oversee new medicines research. These issues must, however, be viewed against a backdrop of major healthcare needs for new and improved therapies for aging populations and for the developing world.

Looking at changing attitudes in science Dr Dere referred to the ethos, from the early 1970s, of "science in the ivory tower"¹ that would provide *true and reliable knowledge* and the four norms required to defend the autonomy of science: Communalism – common ownership of scientific discoveries; Universalism – claims of truth evaluated in terms of impersonal criteria; Disinterestedness – scientists are rewarded in ways that are perceived as "selfless"; and Organized scepticism – rigorous scrutiny within the scientific community.

This era, in which there was little public scrutiny, has largely been replaced by an ethos of "What is science good for, and is it good enough to serve these purposes?"² which is characterised by four norms: mission-orientated research, cross-disciplinary approaches, institutional diversification, and perhaps the most significant, growing public demands for accountability.

Transparency in public science requires a balance between reasons and limits. Developing principled approaches to maintain the desired balance is a problem for contemporary law and policy makers. Total transparency is not always desirable as the scientific process depends on a certain amount of unrestricted trial and errors as well as on competitiveness among peers. Excessive or premature demands for public disclosure may hamper creativity or produce disincentives for high-risk research. Considerations outside science, such as privacy of research subjects, are important constraints of disclosure.

Dr Dere suggested that *collaboration* should be fundamental to the discussions at this Workshop and referred to the five key principles set out in the slide³. In the current era collaboration is critical to development and mandatory for the improvement in productivity that the public is demanding.

COLLABORATION

- **You can't corner the market on smarts.**
 - "None of us is as smart as all of us"
- **Many heads are better than one**
 - Two people have a greater diversity of thought processes, training and experiences than one does, and three beats two.
- **Diversity of thought matters**
 - Everyone seeks and receives the same "solutions" from the same sources, and qualifications can act as constraint to creativity.
- **Openness is risky but necessary**
 - Companies that develop cultures based on secrecy may ultimately hamper the all-important ability to collect new ideas outside of their environments.
- **Open collaboration is here to stay**
 - Internet as the basis of sharing knowledge and power.

Ref: Alph Bingham, www.cio.com

¹¹ Robert K. Merton, *The Sociology of Science: Theoretical and Empirical Investigations*, 1973, The University of Chicago Press

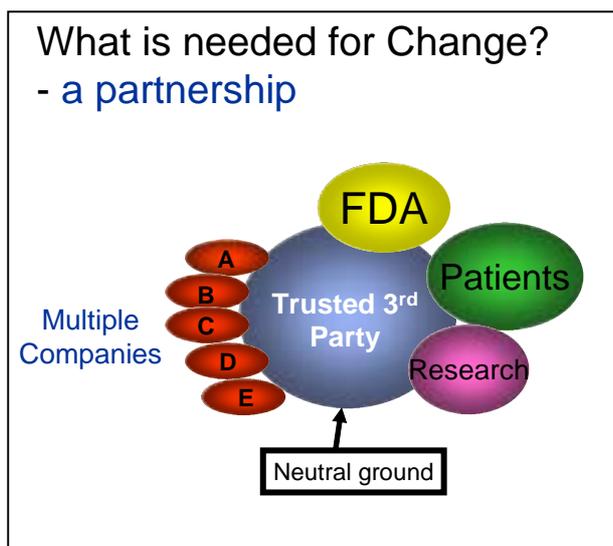
² Sheldon Krinsky *Science in the Private Interest: Has the Lure of Profits Corrupted Biomedical Research?* Rowman and Littlefield, 2003 (pp. 247). ISBN 0-74251-479-X

³ *Five Things Alph Bingham Has Learned About Collaboration*, 22 June 2007, www.cio.com

Companionship on the Critical Path

Dr Jeffrey Cossman, Chief Science Officer
The Critical Path Institute, USA

The Critical Path Institute (C-Path) was developed to support the US Food and Drug Administration (FDA) in the implementation of the *Critical Path Initiative*⁴. A memorandum of understanding has been signed with FDA setting goals for “improved methods for testing new medicinal products” and “effective collaboration among government academia and the private sector”. C-Path represents neutral ground between multiple companies, the FDA and patients in order to share the science of medicines research. Its funding infrastructure involves no direct funding from companies as company members of consortia contribute by carrying out work on projects.



A major priority for C-Path is the development of predictive biomarkers. Biomarkers are needed to tailor therapies, especially in those cases in which therapy is effective only in a fraction of patients. As an example, epidermal growth factor receptor (EGFR) inhibitors are effective, but only in 10% to 20% of patients. It is clear that reliable biomarkers are needed to identify potential responders. Biomarkers also have a role in preventing drugs from being administered to the wrong patient. Approximately 20% of human epidermal growth factor receptor-2 (HER-2) assays to determine the treatment for breast cancer performed were found to be incorrect when the same specimen was re-evaluated in a high volume, central laboratory. This could mean that 15,000 patients per year have incorrect test results.

The FDA has a vision of combined drug and diagnostics submission including a standardized data submission process, best-of-class methods, and proof of reliability and performance. In practice, however, the FDA currently considers drugs, diagnostics, and devices as separate entities handled through separate departments and procedures.

An example of a C-Path project is the National Cancer Institute (NCI) Companion Diagnostics Trial, which involves 1200 patients with lung cancer, with a goal of identifying patients whose tumours will respond to epidermal growth factor receptor (EGFR) inhibitors (e.g., Tarceva®). Twelve diagnostic companies are involved in a process in which they will compare technologies, correlate outcomes, and inform the FDA of their results.

Warfarin is another example of a C-Path project. Warfarin’s dosing is crucial because either over- or under-dosing can cause stroke, embolism, or haemorrhage. Warfarin causes 40,000 emergency visits per year (US) and costs of \$2 billion in adverse events. Many adverse events are left untreated because of toxicity. About 30% to 50% of dose variability is due to genetic variants, such as in CYP2C9 metabolism and VKORC1, which is a drug target. To support a label change on warfarin, the FDA needs gene test evidence. Warfarin could represent a model for gene-drug combinations. The purpose of the National Heart, Lung, and Blood Institute (NHLBI) Warfarin Clinical Trial, which involves 2000 patients, is to genotype patients prior to initial dose administration. The 8 companies involved with running the diagnostic tests are examining the technical validation, clinical utility, and reimbursement.

An area of particular concern where C-Path has recently achieved a major step forward is in the prediction of drug toxicity. Pharmaceutical companies have innovative but different tests to predict

⁴ *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products*, Published by the US Department of Health and Human Services and the FDA, March 2004, www.fda.gov

toxicity but their methods are not independently validated. It was apparent that a standardized approach and best-of-class strategies are needed.

The Predictive Safety Test Consortium (PSTC), established by C-Path to address the problem, is an example of the collaborative culture that must exist to modernize the drug development process. It is an international endeavour that involves input from 190 scientists every month. The PSTC works in teams that focus on specific targeted areas, such as kidney, liver, vasculature, and muscle. The PSTC team working on nephrotoxicity has agreed on 7 consensus biomarkers for kidney damage that were submitted to FDA and the EMEA in 2007 and have subsequently been accepted by these agencies⁵.

Discussion points:

- The process of bringing the nephrotoxicity biomarkers to the clinic through clinical studies has begun and involves 15 pharmaceutical companies as advisors. These consortia partners are considering moving into shared clinical studies to standardize safety and efficacy markers.
- A new effort to standardise laboratory diagnostics is being formed. The United States Diagnostics Standards (USDS) will be an 'Underwriter's Laboratory' for diagnostics. New diagnostic tests will be evaluated by this neutral facility for their performance and utility prior to submission for regulatory approval, implementation as laboratory-developed tests or reimbursement.

What Is the Regulatory Role in Opening up the Knowledge Base?

Professor Bruno Flamion

Chairman, EMEA Scientific Advice Working Party

Professor Flamion expressed the view that, while regulatory bodies have an important role as partners in opening up the knowledge base and encouraging greater openness in innovative development, they should not be in the "driving seat". He discussed the topic by reference to his work with the European Medicines Agency (EMA) and within the context of the European Commission (EC).

The role of the EMA's Committee for Medicinal Products for Human Use (CHMP) in improving knowledge sharing includes: greater transparency, a wider dissemination of information from its scientific advice programmes, involvement in starting new scientific initiatives, and international cooperation through harmonisation programmes such as ICH.

Transparency is seen as crucial for ensuring the sharing of information by regulatory agencies and EMA contributes through published guidelines and European Pharmaceutical Assessment Reports (EPARS). The agency has recently started providing reasons for product withdrawals or negative opinions on applications. Currently, the post-authorisation commitments attached to conditional authorisations are made public but there is a question of whether risk management plans associated with standard authorisations should not also be given wider transparency.

In terms of wider access to information from the scientific advice programme, individual advice is likely remain the typical method since confidentiality must be maintained for product-related issues, but opinions on broader issues can be disseminated through Q&A documents.

⁵ FDA News, Press release, FDA, *European Medicines Agency to Consider Additional Test Results When Assessing New Drug Safety* 12 June 2008, <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01850.html>

Other examples of increasing transparency are the regular EMEA-academia-industry workshops held on topics such as biomarkers, adaptive trial designs, modelling and simulation in paediatrics. EMEA has also published a new reflection paper on benefit-risk assessment methods⁶ which gives greater insight into the way in which decisions on new products are made.

The Innovative Medicines Initiative

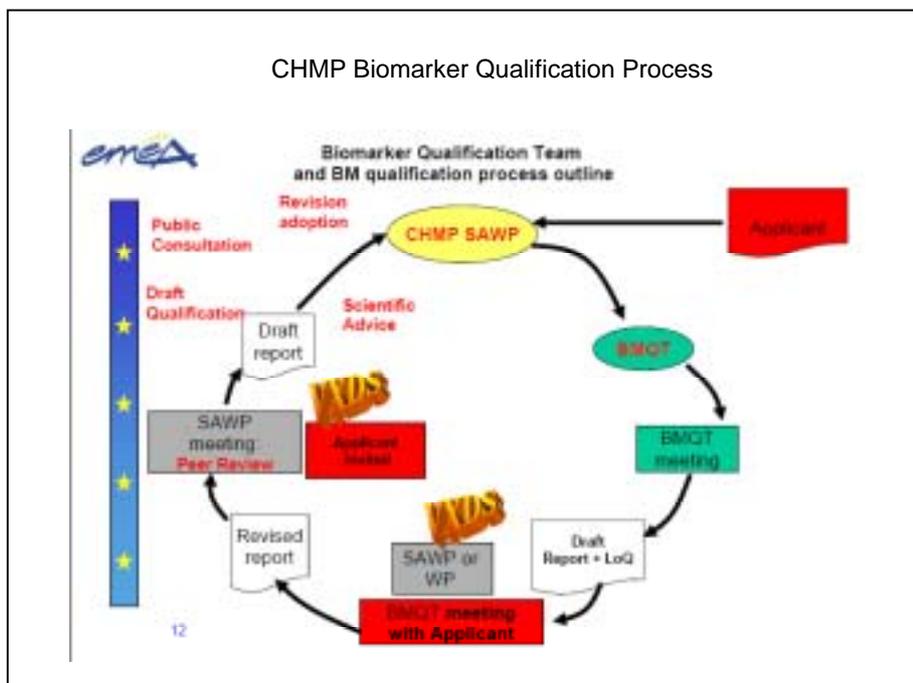
The Innovative Medicines Initiative (IMI) is an example of a new scientific initiative in which EMEA will be in direct partnership on some projects (e.g., pharmacovigilance), and indirectly involved in others such as in discussion forums for early biomarker and the development of new research tools.

The IMI is one of 6 Joint Technology Initiatives (JTI) under the 7th Framework Program of the EC and is a novel type of pan-European public-private partnership. The total budget will be €2 billion for the period 2007-2013 with €1 billion from EC, and €1 billion from the European Federation of Pharmaceutical Industries and Associations (EFPIA) members, provided by work carried out *in kind* and not as direct funding. Community funding will go exclusively to small and medium enterprises (SMEs), non-profit organisations, academia, authorities, clinical centres, or patient organisations established in Europe.

The IMI Joint Undertaking (JU) has set many scientific priorities for 2008 with regard to safety and efficacy. An example of a priority is “Strengthening the monitoring of Benefit/Risk of medicines.” The goal is to facilitate the application of existing data sources, expedite the generation of more reliable pharmacoepidemiological data, explore new methodologies in pharmacovigilance, work towards common standards, and harmonise healthcare databases and patient registries.

EMEA is planning several projects with the IMI. These plans focus on 1) direct partnership in some projects (e.g., pharmacovigilance), and 2) indirect involvement via discussion forums for early biomarker and new tools development, improved scientific advice procedures, and biomarker qualification process in parallel with the FDA.

With regard to EMEA involvement in these projects and future projects, it is very clear that the primary role of the EMEA is the protection of public health and that any partnership with industry must be tightly monitored.



Abbreviations

SAWP: Scientific Advice Working Party

VXDS: Voluntary Exploratory Data Submission

BMQT Biomarker Qualification Team

LoQ: List of questions

⁶ Reflection paper on benefit-risk assessment methods in the context of the evaluation of marketing authorisation applications of medicinal products for human use, EMEA/CHMP/15404/2007, 18 March 2008, available via www.emea.europa.eu

Safety biomarkers

Professor Flamion referred to new procedures agreed by CHMP for the qualification of biomarkers⁷ that had been piloted in 2007 within the framework of the Joint FDA/EMA Voluntary Genomic Data Submissions (VGDS) agreement (with PMDA observers). Agreement had been reached⁸ on the seven nephrotoxicity biomarkers submitted by the C-Path PSTC Consortium previously discussed by Dr Cossman.

Discussion points

- There is an ongoing EMA pilot study examining the benefit-risk assessment process; six products have been selected for review under this process.
- There is full endorsement of the seven biomarkers for nephrotoxicity by the FDA and EMA and data based on these will be accepted for review by FDA and/or EMA.
- Other pre-clinical biomarkers will need to be validated through a similar, transparent process.

Clinical Research Transparency: Perceptions, Progress and Promises

Dr Craig Metz

Vice President, US Regulatory Affairs, GlaxoSmithKline, USA

There are many issues facing drug development and one is the poor public perception of the industry and lack of trust that has led to the current need for greater clinical research transparency. This loss of public confidence, which extends beyond the pharmaceutical industry to the FDA itself, has led to a need to assure compliance through legislation and enforcement. There is no longer an 'honour system', Dr Metz commented.

Through the FDA Amendment Act⁹ Congress has established mandates not only for a registry of clinical trials but also for results to be included in clinical trial databases. Requirements are applicable to both publicly and privately funded trials. By September 2008 the NIH must establish a clinical trial results database and by 2010 this may be extended to include lay summaries that cannot be misleading or promotional. Penalties for non-compliance could be up to \$10,000/day.

There are guiding principles for improving clinical research transparency that include informing the medical and academic research community of ongoing research and providing the opportunity for prospective study subjects to participate. Access to information should help prevent unnecessarily study duplication and promote collaboration with industry. Other principles are to provide a reference point for monitoring study result posting, and provide public access to study results free of charge.

In January 2005, the industry associations, IFPMA, EFPIA, PhRMA and JPMA released Joint Principles for disclosure of clinical study results as summarised in the slide.

Joint* Principles for Disclosure Providing Study Results

Results to be publicly posted for:

- Trials completed on/after 7 Jan 05
- **Non-exploratory** clinical trials
 - Drug approved/marketed
 - Within 1 year of first approval or trial completion
 - Unless publication or local law is compromised
- Exploratory studies with marketed products if:
 - Results regarded as "medically important"
 - Could impact product labeling
- Failed investigational classes/compounds

* PhRMA, EFPIA, JPMA, IFPMA

⁷ EMA/CHMP/SAWP/72894/2008-CONSULTATION, CHMP Draft biomarkers qualification: guidance to applicants, 24 April 2008 available via www.emea.europa.eu

⁸ EMA/250885/2008: CHMP Final report on the pilot joint EMA/FDA VXDS experience on qualification of nephrotoxicity biomarkers, 23 May 2008, available via www.emea.europa.eu

⁹ Food and Drug Administration Amendments Act of 2007, available via www.fda.gov

GlaxoSmithKline (GSK) have established their own Clinical Study Results Database (CSRD) that provides an easily accessible repository of results from GSK-sponsored clinical trials (<http://ctr.gsk.co.uk>). It supplements communications in journals, scientific meetings, healthcare professional letters, and approved prescribing information. Access to this database is unrestricted and includes all trials of marketed products completed since December 2000, giving Phase 1-4 results for approved products. Post-approval studies are posted within 10 months of completion in nearly all cases.

GSK posts ICH-E3 formatted study summaries and lists associated publication citations. These summaries are scientific and non-promotional. As of December 2007, GSK had posted 82 products and 3087 individual study summaries.

Site utilisation

The company has been examining its CSRD site utilization: method of access, number of visits, number of pages the visitor examines, and the length of time spent on the database. They have found that corporate websites have been the leading route to GSK CSRD access. A study of data from January 2005 through June 2006 showed an increase in site visits although, in most cases, the number of CSRD pages viewed per session has remained under 10, and the time per session was under 10 minutes.

Site access using internet-based search engines has increased over time but the vast majority of CSRD site interactions last less than 60 seconds and view fewer than 6 pages. Nonetheless, the absolute number of “meaningful” site interactions is estimated to have exceeded 50,000 since the launch of the site.

Use of data

Some of the anticipated ways in which these clinical trial results and reports will be used are to: conduct meta-analyses and reviews, re-analyze individual study data, inform clinical programs by industry, review manuscripts by editors, and better guide and inform treatment decisions at the physician and patient levels. However, some unanticipated issues have arisen as results may be used to confirm/explore overall benefit/risk, by tort attorneys and State Attorneys for litigation, as well as by journalists to demonstrate incomplete compliance with commitments or governing legislation.

Questions yet to be resolved on the value of increased clinical research transparency include how to measure the overall value/impact on academia, investigators and patients. Other issues are the impact on clinical practice and whether practitioners need training to use these new information sources.

In the Avandia® (rosiglitazone maleate) case, issues arose regarding the potential for an increase in cardiovascular events. Data was provided to the FDA and numerous meta-analyses were carried out by different parties. The public debate was focused on the interpretation of the data and this case study can be seen as a harbinger of the future, where multiple competing and conflicting meta-analyses with different methodologies, limitations, and interpretations can confuse the scientific and lay communities.

Access to raw data

There are calls for access to raw data but there are numerous issues surround its provision. A research framework is needed (e.g., who wants the data, what will it be used for). Also, a definition of raw data is needed (e.g., SAS datasets). Technical support will need to be provided in a standard format. Data analysis and interpretation will need oversight to ensure accuracy and appropriate interpretation. Some companies, including GSK, already provide raw data in response to a research proposition but first and foremost confidentiality of data needs to be preserved, especially in relation to the identity of patients.

Discussion:

- In Europe, more clinical trials are moving to countries outside the EU. There are several issues of concern that involve whether these trials are using GCP, if data are generalisable to other populations, Adverse Event reporting could be different, patient-reported outcomes could vary due to cultural reasons, and study participants may not report AEs appropriately out of a desire to stay in the drug study.
- Health technology assessment bodies and third-party payers should be included when discussing the stakeholders who may be concerned with the development of clinical trial databases.
- Confidence in peer-reviewed journals as a source of respected information although this has been affirmed by the International Committee of Medical Journal Editors (ICMJE). The journals need to evolve their processes and roles, including the valid interpretation of information.

Sharing Pre-marketing Research Data in the Interests of Safety

Sharing Preclinical Data: 'To Share or Not to Share'

A Company Viewpoint

Professor Tim Hammond

Vice President, AstraZeneca, UK

Several factors drive the preclinical data-sharing debate. Adverse drug reactions (ADRs) are a leading cause of death in the US and it is suggested that this could be better addressed through the use of large patient databases. A collection of information from unpublished preclinical studies could provide a platform for sharing data as a confidential database accessible to regulators.

There have been calls for results of toxicology studies to be made available to the scientific community as a result of several high-profile drug withdrawals. It is, however, under debate whether any of these would have been prevented by greater scientific review of preclinical data prior to marketing.

The legal position surrounding sharing preclinical data, for example through consortia, involves anti-trust components but these are surmountable. This is based on the premise that the goal is to improve public health and that the results will be published.

Problems can arise, however, from the premise that all companies will share data equally. There may be a handful of companies that participate in consortia in order to gain information for their own competitive advantage and this is a major disincentive to those companies that are prepared to participate wholeheartedly.

Data sharing can impact the competitive position, particularly in relation to generic competition if data sharing has an impact on data exclusivity and patent protection. Everything in the public domain is used to contest patents, especially in the US. Unlike clinical data, preclinical data are currently very difficult to access and therefore reference. Sharing preclinical data could be a disincentive to product lifecycle developments such as use of new polymorphs supported by new preclinical efficacy and safety data.

Preclinical Data Sharing

- What is driving the debate?
 - High profile drug withdrawals
 - Would these have been prevented by greater scientific review of preclinical data prior to marketing?
 - Exanta – no evidence of hepatotoxicity in any preclinical species
 - Safer Clinical Trials*
 - Phase 1 – Pre TGN1412 considered to be very safe
 - Phase 2/3 – Profile of ADR's primarily reflect pharmacological target

* Source – Academy of Medical Science Report

5

AstraZeneca 

Whilst data sharing could be a benefit to another company in a race and could also save time by avoiding studies already tried by competitors, there are ethical issues in avoiding redundant and duplicative studies. The “good of science” is also a fundamental driver.

What should be shared and with whom?

There is discussion about which data should be shared. Many options exist including the sharing of toxicology data, therapeutic targets, therapeutic concentrations, safety margins, and pharmacological dose response.

The recipients of data sharing include the public. Since data are often complex and interpretation is difficult, companies could face many misinformed questions that could come from patient organisations, animal rights organisations, journalists, and market analysts.

Regulators would also be interested in data sharing. Legislative action from regulators could be a major driver because without such obligations or other incentives, it is unlikely that companies would volunteer to be the first to participate. Regulators could share data among themselves but not enter these data into the public domain.

The mechanisms for sharing pre-clinical data could involve the creation of an international database but this poses many problems. Ideally, it would need a medical lexicon, audit of data, full disclosure, information technology (IT) solutions, and be a ‘safe haven’ for posting data. Another mechanism for greater transparency might be to post Investigator’s Brochures on company websites but this would be helped by a defined format and a common level of information.

To a large extent, regulators hold the key as they already have access to all data submitted as part of regulatory submissions and, to a certain extent, on compounds that fail during clinical development. They also have knowledge on mechanisms of action of terminated products and could prevent wasteful research on mechanisms doomed to fail. Regulators and industry would, however need to work out ways to highlight problematic areas in order to encourage discussion of pre-competitive research in a public forum.

Dr Hammond concluded with a reminder that patient safety must always come first. Greater data sharing should happen, but not in a way that makes the industry, which is already struggling, lose innovation.

Discussion:

- Data sharing has yet to happen with compounds that fail and scientists would have to check with their respective legal offices about whether to share data surrounding failed compounds.
- Since the structures of companies are different, pre-clinical data would not be in the same format, although formats may be more similar in first-in-man (FIM) studies.
- The correlation of pre-clinical studies and clinical outcomes has been studied but this did not include those studies that didn’t make it to man. Similarly, there are efforts to examine products withdrawn in the post-market stage for reasons that could be related to preclinical signals.
- Translational medicine/research, where studies move from the clinic back to the research bench (and *vice versa*) is increasingly being used to study mechanism and differing patient responses. Examples were cited from the statins (development of rhabdomyolysis) and mutations of epidermal growth factor receptor (EGFR) kinase receptors.

Sharing Research Data: An Agency Viewpoint

Dr Andrew French

Group Manager Licensing Division, MHRA, UK

The TGN1412 incident in March 2006 resulted in an in-depth review of clinical trials and their conduct. The Secretary of State for Health set up an Expert Group, and a wide range of stakeholders provided contributions to the Working Group.

A key finding of the Expert Group was that there is value in setting up a mechanism whereby information on previous clinical trials, particularly where there were adverse effects, could be shared at least by regulators, if not the wider research community.

A balance needs to be achieved between placing information in the public domain and maintaining confidentiality in areas that may be commercially sensitive. Also, the issues of who would maintain such a database and how it would be policed to ensure that it was comprehensive are key concerns. To date, there has been progress mainly in the exchange of information between regulators.

Exchange of information



- The exchange of information between the MHRA and the competent authorities in other EU Member States at the time of clinical trials occurs in a number of different ways.
- The Clinical Trials Facilitation Group (CTFG) has undertaken several initiatives to extend the sharing of information across Member States. Examples of these are
 - Monthly teleconferences amongst interested Member States to discuss safety issues arising from trial applications and in terms of on-going trials
 - Meetings of assessors in the three disciplines on a pan-European basis
 - Nonclinical assessors met in Paris in February
 - Pharmaceutical assessors will meet in Sweden in September
- The EudraCT data base will be updated to allow assessment reports from the individual countries to be available to assessors in all Member States

The exchange of information occurring at present is in 3 main areas: 1) between the Medicines and Healthcare Products Regulatory Agency (MHRA) and Research Ethics Committees (RECs), 2) between the MHRA and FDA, and 3) between competent authorities in the EU Member States.

The exchange of information between the MHRA and RECs allows the licensing authority and individual ethics committees to disclose to each other any information that may assist the other party in carrying out its functions under the regulations.

The exchange of information between the MHRA and the FDA involves the sharing of relevant information such as safety information.

The exchange of information between the MHRA and the competent authorities in other EU Member States (MS) occurs in different ways. The CHMP provides a forum for such exchange at time of licensing and following the marketing of products.

There is also an exchange of information between the MHRA and the other EU MS at the time of clinical trials. The Clinical Trials Facilitation Group (CTFG) has undertaken several initiatives to extend the sharing of information across EU MS such as monthly teleconferences amongst interested MS to discuss safety issues arising from trial applications and on-going trials. Another example is the EudraCT database that will be updated to allow assessment reports from individual countries to be available to assessors in all Member States.

There is currently an ongoing project within the CTFG to look at a method of providing a more harmonised assessment of multi-national trial applications. One area being developed relates to FIM studies that are carried out on a multi-national basis with compounds that are classified as 'potential high-risk medicinal products' according to the CHMP Guidelines¹⁰.

In conclusion, the need for information to be shared between regulators has been identified and steps are in place to address this need. Communication channels for regulators have been established and are being developed, particularly within the EU.

¹⁰ Ref: EMEA/CHMP/SWP/28367/2007 Corr, Guideline on requirements for first-in-man clinical trials for potential high-risk medicinal products, 22 March 2007, available via www.emea.europa.eu

Discussion:

- A major problem that regulators face is the increasing volume of requests for the release of clinical and preclinical data under freedom of information acts.
- Companies must take on more of the burden of releasing such data or the EMEA will be overwhelmed by such requests to the detriment of reviews. Trained assessor is needed to know which information is sensitive (e.g., confidentiality, privacy) and this cannot be handled at an administrative level.
- Sharing information and data sharing are often discussed without specifying the level at which this might take place – i.e., the granularity.
- The time allowed for research ethics committees to decide on clinical trials is very limited, especially for FIM studies, and they often need to rely on the scientific opinions of the regulatory authority to support their deliberations.

SESSION 2: FACILITATING CO-OPERATION AND KNOWLEDGE SHARING PRE-MARKETING

Introduction

Dr Supriya Sharma

Director General, Therapeutic Products Directorate, Health Canada

Dr Sharma introduced the second session with a brief analogy from her recent travels in which she had seen ‘a lot of walls’. In times of stress and pressure, people tend to look inwards and build walls instead of looking outwards and building bridges. The walls and barriers to sharing information included intellectual property and the need to define a ‘non-competitive space’ but the presentations from the earlier session had been about building bridges to overcome these. The discussion was no longer about ‘whether’ collaboration should take place; the question at the forefront is ‘how’ to collaborate and share data.

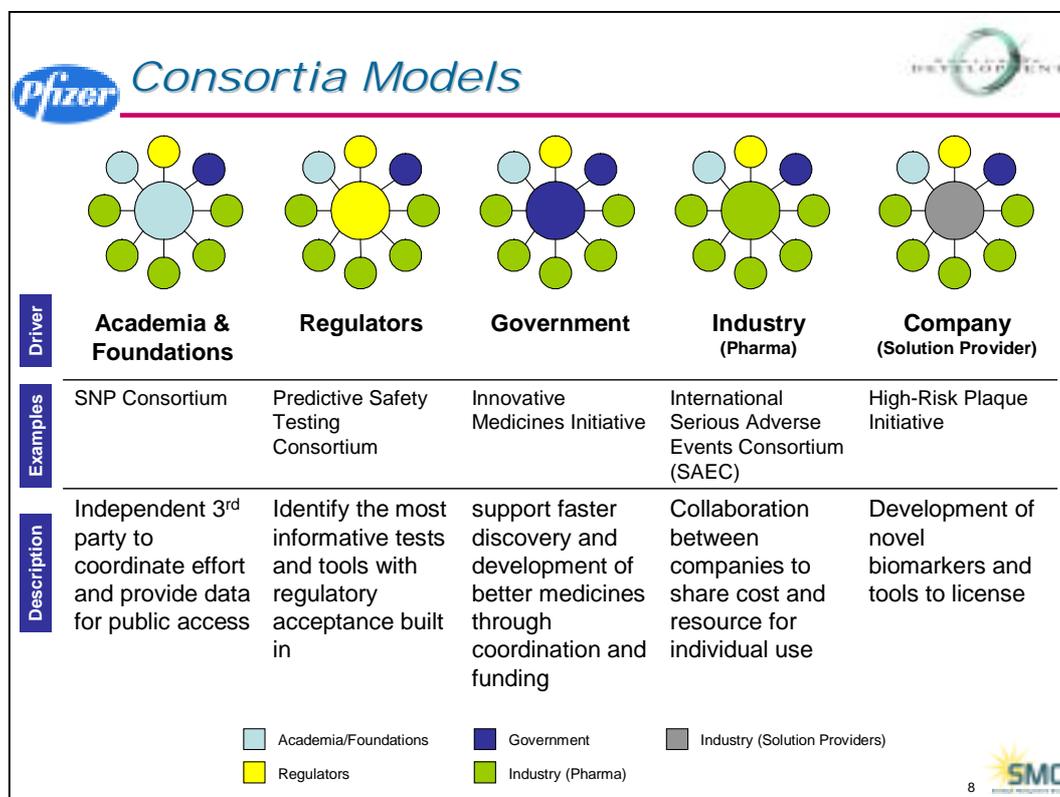
Increased Co-operation as the Key to Developing Clinical and Regulatory Pathways for New Disease Treatments

Dr Liam Ratcliffe

Senior Vice President, Neurosciences, Pfizer Inc, USA

Dr Ratcliffe looked at the origins of, and need for, consortia as part of current pharmaceutical R&D and gave a view on future developments. There are currently over 40 consortia and public-private partnerships focused on discovering and developing new medicines compared with less than 10 seven years ago. The growth must be seen against the background, discussed earlier in the Workshop, of increasingly complex drug development, rising costs of R&D and a falling number of new molecular entities (NMEs) reaching the patient. An important driver, however, is the need for greater transparency and the acceptance by regulators and practitioners of the standardisation and use of new technologies and endpoints. In the consortia landscape today, different needs are addressed; many are focused on specific diseases or therapeutic areas whilst others address the need for better safety or efficacy testing. Funding can range from \$50K to \$320m. Many of the hurdles faced by consortia have been largely overcome, including legal issues of intellectual property rights and anti-trust regulations but common challenges include governance and decision-making, liability in matters relating to safety, logistics and the ability to deliver on time.

Different structural models are illustrated in the slide which gives examples of the main drivers for consortia: Academia and foundations; Regulators; Government; The pharmaceutical industry; and Other companies that are 'solution providers' seeking recognition of the 'problem. Examples of the latter are developers of novel biomarkers and diagnostics for validation and incorporation into development and regulation.



The different participants and players have overlapping and divergent interests from academic interests in exploring science and studying rare diseases, to government drivers of economic stimulation and support for research enterprises, to the industry need to speed up drug development, contain costs and gain regulatory acceptance. The overarching goal for all participants, however, is to increase the flow of new medicines.

Dr Ratcliffe reviewed examples of different types of consortia:

- MATRICS-CT¹¹: looking at ways to measure cognitive enhancement in the treatment of Schizophrenia in terms of its translation into a 'community outcome' where the individual is able to function in society;
- The Predictive Safety Testing Consortium (PSTC) established by Critical Path Institute (C-Path) and eight pharmaceutical companies to cross-test preclinical laboratory methods to determine which are most effective in detecting kidney, muscle, and liver toxicity¹²;
- The Oncology Biomarker Qualification Initiative formed by the FDA, the National Cancer Institute (NCI), and the Centers for Medicare and Medicaid Services (CMS) which is evaluating whether Positron Emission Tomography (PET) scans can provide a marker for early drug response in non-Hodgkin's lymphoma.
- The International Serious Adverse Events Consortium (SAEC) formed by heads of R&D from several major pharmaceutical companies to investigate *inter alia* if there is a genetic basis for serious adverse reactions to drugs.

¹¹ MATRICS-CT (Measurement and Treatment Research to Improve Cognition in Schizophrenia: Co-primary identification and Translation of the Battery)

¹² See also presentation by Dr Jeffrey Cossman, C-Path, page xx of this report

Regulatory involvement in Consortia is particularly important in identifying the direction that research should be taking and improving the acceptance of biomarkers and clinical endpoints through early endorsement and engagement. This is of particular value when outcome measures are for use in international trials.

Future directions

The end of the intensive growth phase in the number of consortia may have been reached and the next phase may be one of consolidation into fewer but better organised consortia in order to ensure that they deliver. Another scenario is that industry's 'pre-competitive space' will increase and the way in which medicines are delivered will be redefined with an emphasis on neglected diseases and a greater involvement of non-profit organisations and Foundations.

The future will be shaped by the extent to which consortia are able to meet their objectives in order that the pharmaceutical industry can see a return on the investment in consortia that is being made.

Discussion:

- Some of the characteristics that define successful consortia are that they have clear goals and objectives, they deliver something meaningful, and are relatively small with strong project management.
- Many products with similar modes of action are often developed in parallel in a 'race' to be first to market with a new therapeutic target. This may be healthy competition but also seems wasteful and duplicative. Consortia may not be the answer and the driver to curb such development will be economic as the payers may not reimburse a third or fourth in class follow-on compound.
- Consortia are standardising industry activities in an increasing pre-competitive space relating to drug development that may previously have been felt to be proprietary. In practice, the unique, patentable, molecular composition remains the strongest competitive advantage.

Safety Biomarkers for Regulatory Decision-Making

Experience from the Novartis-FDA-CRADA and Engagement with the Predictive Safety Testing Consortium

Dr Joanne Meyer

*Vice President and Global Head, Biomarker Development
Novartis Pharmaceuticals, USA*

Note: Dr Meyer was prevented, at the last minute, from attending the Workshop but copies of her slides were made available to participants and the following abstract was subsequently provided.

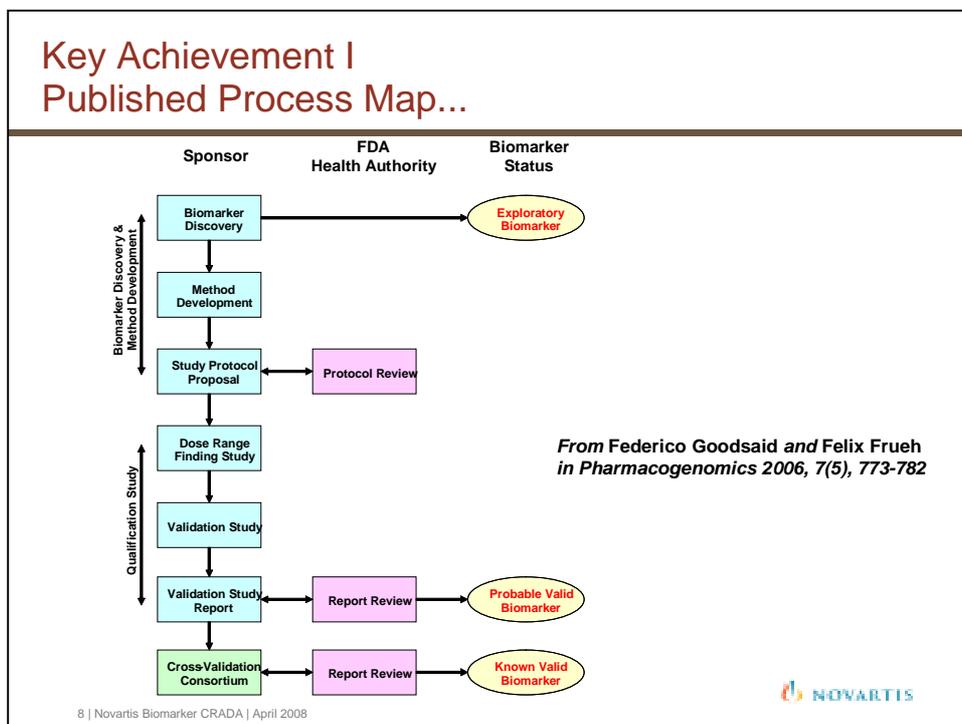
Presentation Summary

- Collaboration produces a framework for qualification of new safety biomarkers which will enhance industry-wide understanding of this important issue.
- Preclinical data identified as part of this process have demonstrated evidence of superiority over the current standards used to assess renal injury in drug testing.

An overview is provided of the cooperative research and development agreement (CRADA) between Novartis and the FDA that has led to a number of key achievements, which will enhance the development and applications of preclinical biomarkers to evaluate drug safety. The CRADA is one of the first projects conducted under the FDA's Critical Path Initiative. The Critical Path Initiative was launched by FDA in 2004 to refine the science and processes through which FDA-regulated drugs, biologics, and devices are translated from a discovery or 'proof of concept' to a medical product.

The FDA-Novartis CRADA had two primary objectives: 1) To define a process for qualifying preclinical safety biomarkers for regulatory decision making; and 2) to test this pilot process by submitting kidney-related safety biomarkers identified and characterized through preclinical studies to the FDA for qualification.

Efforts conducted under the CRADA have resulted in the publication of the first pilot framework for a preclinical regulatory biomarker qualification process¹³. The development of this process will have a broad impact on the understanding of the qualification of safety biomarkers far beyond this partnership.



In addition, the preclinical data identified thus far have demonstrated evidence for the superiority of new renal biomarkers over the current standards used to assess renal injury in drug testing, namely serum creatinine and blood urea nitrogen (BUN). Further efforts will focus on the extended clinical qualification of biomarkers that could allow clinicians to detect kidney injury in patients earlier than current clinical practice allows.

Relevant safety biomarker data generated by Novartis as part of the CRADA has been shared with the Critical Path Institute's Predictive Safety Testing Consortium (PSTC). The PSTC is a larger public/private partnership between industry, academia, and regulatory health authorities intended to serve as a neutral body for coordinating activities related to biomarker qualification in drug development.

The CRADA data, together with data generated by other partners in the PSTC has been submitted to FDA and the European Medicines Agency (EMA) as part of a Voluntary Exploratory Data Submission (VXDS). As a result of this data submission, FDA and EMA have utilized internal boards and worked to refine the process to qualify such preclinical safety biomarker data. Further joint evaluation of additional data under the auspices of the PSTC is expected to lead to additional submissions of peripheral biomarkers representing additional renal pathologies.

¹³ From Federico Goodsaid and Felix Frueh in Pharmacogenomics 2006, 7(5), 773-782